Abbott

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November 10, 2006

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: **Docket No. 2006D-0344**
Draft Guidance for Industry on Drug Interaction Studies: Study Design, Data Analysis, and Implications for Dosing and Labeling

Abbott Laboratories is pleased to provide the following comments on the draft guidance for industry entitled, "Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling," published in the *Federal Register* on September 12, 2006.

1. **Line 140 [Section II, part 2 ("Transporter-Based Drug-Drug Interactions")] describes transporter-based interactions and, by reference to Appendix A (see line 672), lists some of the major human transporters and known substrates, inhibitors, and inducers.**

    a. Please modify this portion of the guidance to identify any specific probe substrates that are acceptable for in vivo transporter interaction assessment. Some of the substrates listed in Appendix A (Table 1) have not been found acceptable by certain review teams.

    b. Consider revising Table 1 in Appendix A to include I/Ki values for each of the listed inhibitors.

2. **Line 234 [Section III, C ("Population Pharmacokinetic Screens")] states "...it is unlikely that population analysis can be used to prove the absence of an interaction that is strongly suggested by information arising from in vivo studies specifically designed to assess a drug-drug interaction.**

    If a population pharmacokinetic analysis is adequately powered to detect differences in pharmacokinetics and no clinically significant interactions are seen in that analysis, but clinically significant interactions are observed in the in vivo studies specifically designed to assess drug-drug interactions, please consider whether the population pharmacokinetic analysis would be sufficient to conclude the absence of clinically significant interactions.

3. **At line 245 [Section IV ("Design of In Vivo Drug-Drug Interaction Studies")], consultation with FDA regarding study protocols is recommended.**

   We recommend the guidance stipulate this consultation is a Type B meeting, to help us better plan development timelines.

4. **At lines 305-316 [Section IV, A ("Study Design")] the sixth bullet recommends certain medication and dietary restrictions to avoid variable study results.**

   Please clarify whether references to a two-week exclusion period in both examples imply a recommendation for a specific timeframe, and if so, provide reference to supporting information. Also, please clarify whether the exclusions listed should be applicable to all or only specific drug interaction studies.

5. **At line 388 [Section IV, C, 1 (fourth paragraph)], the guidance describes the simultaneous administration of a mixture of substrates of CYP enzymes in a single study (i.e., a "cocktail approach") as one way to evaluate a drug's inhibition or induction potential. According to the draft guidance, positive results in such a cocktail study can indicate the need for further in vivo evaluation, if the initial evaluation only assessed the changes in the urinary parent to metabolite ratios.**

   a. Please include examples describing when the cocktail approach might be useful or preferred, as well as examples of cocktails accepted by FDA.

   b. Please clarify whether further studies are also necessary if a positive cocktail study evaluates plasma levels instead of urinary ratios.

6. **Line 449 [Section IV, C, 2 ("Investigational Drug as a Substrate of CYP Enzymes")] notes there may be situations when an evaluation of the effect of multiple CYP inhibitors on the investigational drug can be informative.**

   It would be useful if the final guidance contained more detail about the evaluation of the effect of multiple CYP inhibitors on a particular investigational drug. For example, please clarify, in situations where a drug is metabolized by multiple enzyme systems, whether there are limits to the number of inhibitors that can or should be evaluated in the same study.

7. **Line 484 [Section IV, C, 4 ("Investigational Drug as a Substrate of P-gp Transporter")] describes ritonavir as an inhibitor of P-gp and recommends that it be used to test an investigational drug for the possibility that its transport may be inhibited.**

   Ritonovir may not be the best choice of a P-gp inhibitor, as its effects appear to be time dependent.

We thank the Agency for its consideration of our comments. Should you have any questions, please contact Ms. Melodi McNeil, Director, Regulatory Intelligence, at 301-255-0085, x105 or by FAX at 301-255-0090.

Sincerely,

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Divisional Vice-President
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